REMARKS

The present invention is directed to a system that allows for automated, real time fluorescent monitoring of multiple samples as they are being subjected to rapid thermal cycling. The novel combination of elements, including 1) the use of thin walled, high surface area to volume vessels, constructed of materials with a high thermal conductivity, 2) the use of fluorescent real time monitoring of the reaction and 3) the use of forced air as the thermal transfer agent, provides a novel system that allows for the simultaneous rapid thermal cycling of a plurality of samples while the reaction is monitored in real time.

The claims have been amended to more clearly define that which applicants believe to be their invention. More particularly, claims 13, 128 and 173 have been amended to specify that the sample vessel comprises walls composed of an optically transparent material and defining a volume wherein the ratio of volume to external surface area of the container is less than 1 mm. Support for that amendment is found throughout the specification and more particularly on page 67, lines 24-28. Claims 79, 82, 121 have been amended to specify that a forced air heater is used to conduct thermal cycling of the biological samples. Support for that amendment is found throughout the specification and more particularly on page 32, lines 5-14 and page 75, lines11-16. Claims 18 and 178 are amended to specify the dimensions of one embodiment of a sample vessel. Support for the amendments to claims 18 and 178 is found throughout the specification, and more particularly on page 19, lines 15-18 and page 21, lines 29-32 and page 22, lines 22-24. Claims 169-171, 194 and 195 are amended to reflect that the sample is being heated at a rapid rate not just the sample vessel. Similarly claims 29, 55, 121 and 128 are further amended to clarify the claim language, and those amendments introduce no new matter.

Allowable Subject Matter

Applicants note that the Examiner has found claims 141, 142 and 153 allowable if rewritten in independent form. Accordingly, independent claim 128 has been amended to incorporate the limitations of claims 141 and 142 and independent claim 152 has been amended to incorporate the limitations of claim 153. These amendments are believed to place claims 128-132, 134-140, 143, 144, 152, 154 and 155 in condition for allowance.

35 USC §112 Rejections

Claim 18 stands rejected under 35 USC § 112, second paragraph as being indefinite. Claim 18 has been amended to specify that the volume of the container is not greater than about 100 ul. The amendment is believed to be responsive to the Examiner's objection and applicants respectfully request the withdrawal of the rejection of claim 18 as being indefinite.

35 USC §012 Rejections

Claims 13-18, 20, 22-35, 55-59, 79, 80, 82, 87-92, 121-125, 128-132, 134,-140, 143, 151, 152, 154-158, 160, 169-188, 191-195 and 197 stand rejected under 35 USC § 103 as being unpatentable over Bouma et al. in view of Jordan. Applicants respectfully traverse.

The present invention is directed to a system comprising multiple elements that have been selected, and combined in a unique fashion, to provide a system that rapidly and homogenously heats and then cools a sample multiple times (i.e. rapid thermal cycling). As disclosed at page 6, line 31, thirty amplification cycles can be carried out in less than 15 minutes using the claimed system. Surprisingly, applicants have determined that rapid thermal cycling has the benefit of substantially increasing the specificity and yield of PCR (see page 18, line 28 through page 19, line 8 and Figs. 6 & 7). It is this discovery that led applicants' to optimize their system, by selecting and combining elements that optimize the speed of thermal transfer to multiple samples, thus resulting in the unique system that applicants now claim as their invention.

The present invention provides a system that allows for **rapid and homogenous** thermal cycling of multiple samples, through the use of 1) sample vessels designed for optimal thermal transfer, 2) selection of a thermal transfer medium that can be rapidly adjusted, and 3) the use of real time monitoring of the reaction. More particularly, the sample vessels of the claimed system have thin walls, are composed of a material exhibiting high thermal conductivity, and have a high external surface area to volume ratio. In one embodiment the sample vessel is a capillary tube, as claimed in claims 18, 33, 80, 125, 145, 151 and 155. In addition, applicants' device uses forced heated or cool air as the thermal transfer medium to allow rapid switching from the heating cycle to the cooling cycle and back again. The prior art fails to teach or suggest this unique combination of elements, nor does it provide any motivation to make such a combination.

Applicants respectfully submit that Bouma et al., failes to appreciate the benefits of rapid cycling, and therefore that reference provides no teaching, guidance or motivation to the skilled practitioner to modify the Bouma device to create a device similar to that claimed in the present application. In particular, applicants note that Bouma state, "However, the details of the method of thermocycling are not critical to the invention" (see page 8, lines 8-9 of Bouma et al.). Furthermore, Bouma et al state that the temperature may be controlled by air or water baths, without providing any rationale for selecting one over the other. Applicants respectfully submit an Examiner must do more than simply note that the various elements of the present invention have been mentioned in the prior art, there must be an objective reason why one of ordinary skill would select the unique combination of elements as claimed in the present system.

When prior-art references require a selective combination to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself. Something in the prior art as a whole must suggest the desirability, and thus the obviousness, of the combination (Uniroyal Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 5 USPQ2d 1434 (Fed Cir. 1988). Here the Bouma reference actually states that it is not important how the thermocycling is conducted, and thus fails to provide any rationale or motivation for selecting forced air as the thermal transfer agent.

The Examiner also contends that Bouma teaches the use of small reaction vessels as claimed in the applicants system. Applicants respectfully traverse and note that while Bouma does disclose the use of small reaction samples, Bouma discloses that the reaction vessels are typically microcentrifuge tubes. As noted by the Examiner, Bouma et al. also state that other vessel configurations are possible, but this vague reference that other shaped vessels may be compatible with their invention provides little guidance to one of ordinary skill in the art. Bouma et al. simply fails to provide any rationale for selecting a vessel having the characteristics of those used in applicants claimed system. In particular, the Bouma reference is devoid of any specific mention of a capillary tube as a suitable reaction vessel, nor does the reference provide any reason for selecting a reaction vessel that has thin walls, is composed of a material exhibiting high thermal conductivity, and has a high external surface area to volume ratio. The mere fact that the Bouma reference envisions "other configurations" does not suggest the use of the vessels as claimed in the present invention, absent some motivation for making such a selection.

Furthermore, on page 8, lines 21-24 of Bouma et al, the authors state that their device shown in figure 1 includes "a distance between the element surface 38 and the walls of the reaction vessel 20 that is sufficiently great to prohibit capillary action of an aqueous sample therebetween." Accordingly, if capillary action does not occur between the external wall of the total internal reflection element and the vessel interior walls when the total internal reflection element is inserted in the reaction vessel, then clearly the reaction vessel of Bouma et al. itself cannot be a capillary tube.

Applicants respectfully submit the Bouma reference fails to teach or suggest the very elements that comprise applicants' novel system. Furthermore, since Bouma et al. openly state that the method of thermocycling is not important to their invention, they provide no motivation to pick and choose the elements of the present invention and combine them in a way that produces the present claimed system; one that is capable of conducting the rapid and homogenous cycling of the vessel contents.

The secondary reference fails to complement the inadequacies of the Bouma reference teachings. Jordan et al. is directed to an automated system for delivering a sample and reagents to multiple reaction chambers. The Examiner contends that Jordan describes a device with a carousel wherein the simultaneous temperature control of the system is provided "as claimed in the present invention." Applicants respectively submit that the Examiner is overstating the teachings of the Jordan reference. The presently claims system requires thermal cycling. Jordan discloses "The last incremental step to bring the liquid in each cuvette vessel to the proper temperature can be provided by maintaining the whole conveyer device, or at least a portion of the upper flight of the conveyer 172, in an enclosure which contains a circulating atmosphere maintained at the selected temperature. Alternatively the conveyer can descend to lower the vessels into a water bath."

Accordingly, Jordan suggests that samples can be adjusted to a single desired temperature through the use of circulating air, or a water bath, maintained at a single temperature. There is no discussion within Jordan regarding the use of thermal cycling of the reaction contents, nor is there any guidance provided for selecting between a water bath or a circulating atmosphere to alter the temperature of the sample. Furthermore, there is no suggestion provided by Jordan regarding the desirability of using thin walled vessels having a high external surface area to volume ratio. The prior art failed to recognize the desirable

attributes of rapid cycling and thus fails to teach or provide any motivation for preparing a system capable of conducting such rapid cycling on samples.

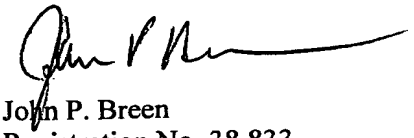
Applicants also note that while Jordan discloses photometric analysis of the reactions conducted within their device they fail to teach or suggest adjusting the reaction conditions means in accordance with the reaction parameter.

The presently claimed system incorporates several components that allow for rapid thermal cycling of samples. In particular, air is used as the thermal transfer agent, and the sample containers are selected to have thin walls composed of material having high thermal conductivity, and a high external surface area to volume ratio (e.g. a capillary tube), to allow rapid thermal energy transfer from the exterior to the sample, and vice versa. The prior art references fail to teach or suggest sample vessels having these features, and furthermore, fail to teach or suggest the combination of the sample vessels with a thermal transfer medium capable of rapid temperature fluctuations. In addition, the presently claimed system comprises a rotating carousel for positioning each container before a fluorimeter assembly while the samples are being subjected to rapid thermal cycling. Accordingly, the present invention allows for rapid thermal cycling while simultaneously conducting real time monitoring of multiple samples. Furthermore, in some embodiments the reaction conditions are altered based on the real time monitoring of the reaction. The present system can do this without requiring multiple fluorescent detectors or requiring the samples to be held in a fixed position.

The claim system must be viewed as a whole, including applicants' recognition of the desirability of rapid cycling that resulted in the unique combination of elements to optimize the simultaneous and homogenous rapid thermal cycling of multiple samples. Focusing on the obviousness of substitution and differences, instead of on the invention as a whole, is a legally improper way to simplify the difficult determination of obviousness. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 USPQ 81, 93 (Fed Cir. 1986). Applicants respectfully submit that obvious to try is not the proper standard to determine obviousness, and absent applicants disclosure there was no motivation for creating the system as claimed herein.

The foregoing claim amendments and remarks are believed to fully respond to the Examiner's rejections. The claims are believed to be in condition for allowance. Applicants respectfully request allowance of the claims, and passage of the application to issuance.

Respectfully submitted,



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